Protecting the Blood Supply from Infectious Threats

Demystifying Medicine
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Disclosures

- **NIH site PI of Hologic Grifols Zika virus nucleic acid test under IND**
- **NIH Blood Bank utilizes the Cerus Corp. Intercept system for pathogen reduction of platelets** (only FDA-licensed system)
- **I do not have financial interests in either**

Learning Objectives

1. Background on US blood supply, indications for transfusion and impact
2. Strategies used to protect the US blood supply from transfusion-transmitted agents, including:
   - Donor selection
   - Blood screening
   - Pathogen inactivation
3. Define current and emerging infectious agents
4. Advantages, Limitations and Impact of these strategies

Background: Blood Supply in the U.S.

Collected and transfused blood in the U.S. every year

Blood Component	Collected (millions)	Transfused (millions)
Whole Blood (RBC)	13.6	6.1
Platelets	2.2	1.3
Plasma	4.3	1.8
Cryoprecipitate	1.3	1.0

- **96% collected by blood centers** (E.g. ARC, BCA); **remaining 4% collected by hospitals**
- **~10,000 donations/year in the Clinical Center DTM**

Ref: 2013 AABB Blood Survey Final Report (2015 Report Pending)

What are the indications for transfusion?

Rank	Condition	No. Hospital Stays Requiring RBC Transfusion
1	Sepsis	174,440
2	Gastrointestinal bleed	171,995
3	Acquired or hereditary anemias*	141,225
4	Hip fractures	87,590
5	Complications of device, implant or graft	81,865
6	Osteoarthritis	79,410
7	Renal failure	54,830
8	Surgical/medical complications	52,205
9	Congestive heart failure	49,365
10	Pneumonia	48,840
11	Myocardial infarction	38,565
12	Diverticulosis and diverticulitis	37,885
13	Heart disease (e.g. CAD)	32,440
14	Acute posthemorrhagic anemia	31,485
15	Heart valve disorders	27,800

Ref: West et al. AHRQ Statistical Brief, Healthcare Cost and Utilization Project 2013

Impact of Blood Transfusion

- **1 in 10 Americans admitted to the hospital require blood**
- **20% of blood supply used for surgeries**
- **15% of blood supply allocated for patients with cancer**
- **4.5 million Americans would die each year without receiving blood transfusions**

Refs: America's Blood Centers (ABC);
2011 National Blood Collection and Utilization Survey Report

Impact of Transfusion-Transmitted Infections

- Death.
  - 14% of transfusion-related deaths
  - 44, Transfusion-Associated Sepsis
  - 8, babesiosis
  - 1, vCJD
  - 1, Malaria
- Severe illness, complications of primary disease, prolonged hospitalization
- Impact outcomes of bone marrow transplantation?
- Birth defects due to Zika-infected blood transfused to pregnant women?

Vamvakas et al, Transfusion-related mortality *Blood* 2009;
FDA Reports, UK SHOT surveillance system, French surveillance system (1996-2007)

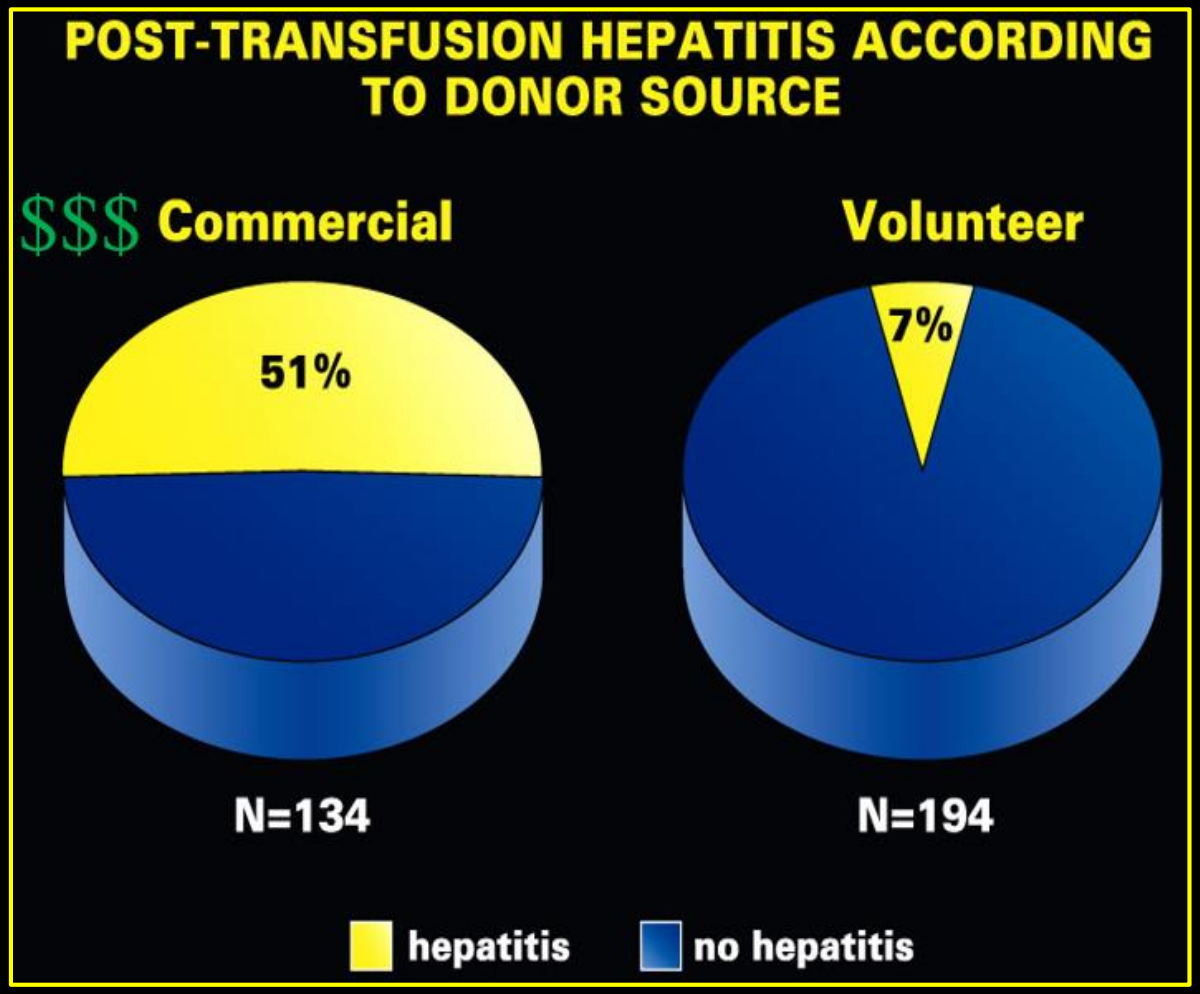
What are the strategies used to protect the blood supply from transfusion-transmitted infections?

The Protective Triad

Slide adapted from Dr. Harvey Alter …beloved scientist but traitorous Red Sox fan! (Arias is excused)

Donor Selection: Volunteer Blood Donors Only

- Prior to February 1970, many blood donors in the U.S. were PAID $$$



- Exclusion of paid donors contributed to a >20% reduction in post-transfxn hepatitis***

Alter et al, NIH HEART Study → still an active, prospective study called TRIPS

Donor Selection: Donor Health Questionnaire

Are you

1. **Feeling healthy and well today?**
2. **Currently taking an antibiotic?**
3. **Currently taking any other medication for an infection?**

- ***Should* eliminate donors with current, symptomatic infections (E.g. 20% of Zika virus infections)**

Donor Selection: Donor Health Questionnaire

In the past 12 months, have you had a/an

18. Sexual contact with IV drug user?

19. For males, sexual contact with another male?

21. Sexual contact with someone with hepatitis?

22. Lived with someone with hepatitis?

25. Had syphilis or gonorrhea?

- **Yes to any of these gets an exclusion from blood donation for 12 months**

  ***New for MSM**

Ref: FDA guidance update, 12/2015

Donor Selection: Donor Health Questionnaire

In the past 12 months, have you been

26. In detention, jail or prison >72 hours?

✓ **No blood donation for 12 months**

Donor Selection: Donor Health Questionnaire

In the past 3 years, have you

27. Been outside the US or Canada?

(i.e., have you been exposed to malaria?)

- **If you've been to a country with malaria, wait 12 months to donate**
- **If you've been infected with and treated for malaria, wait 3 years to donate**

Donor Selection: Donor Health Questionnaire

From 1980 through 1996

28. Did you spend 3 months or more in the UK?

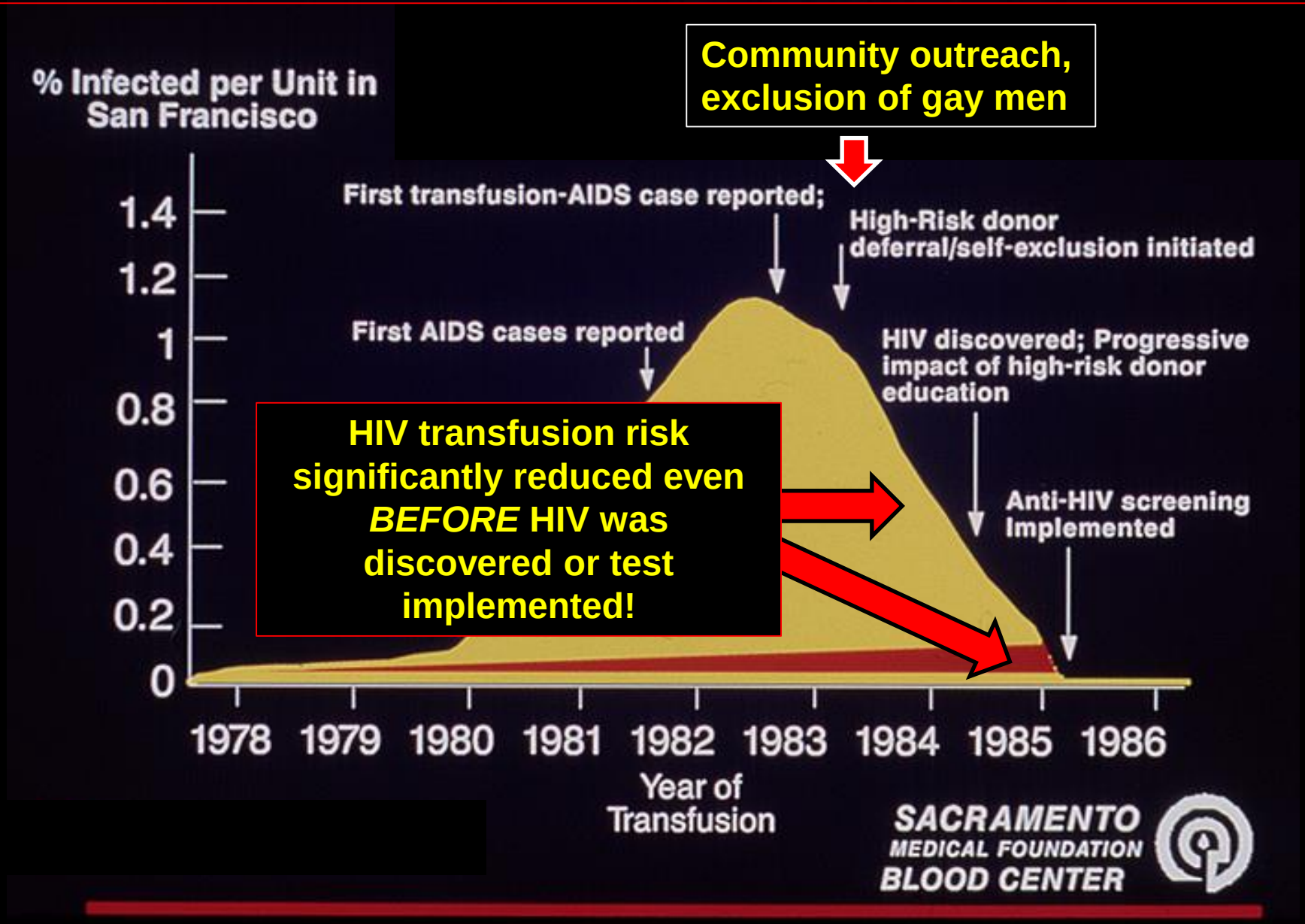
From 1980 to the present

30. Did you spend time that adds up to 5 or more years in Europe?
31. Receive a blood transfusion in the UK or France?

- Yes to any of these excludes you from blood donation for life due to risk of variant Creutzfeld-Jacob disease (vCJD)

Donor Health Questionnaire may not seem like sexy science (most good public health interventions aren't), but it works…

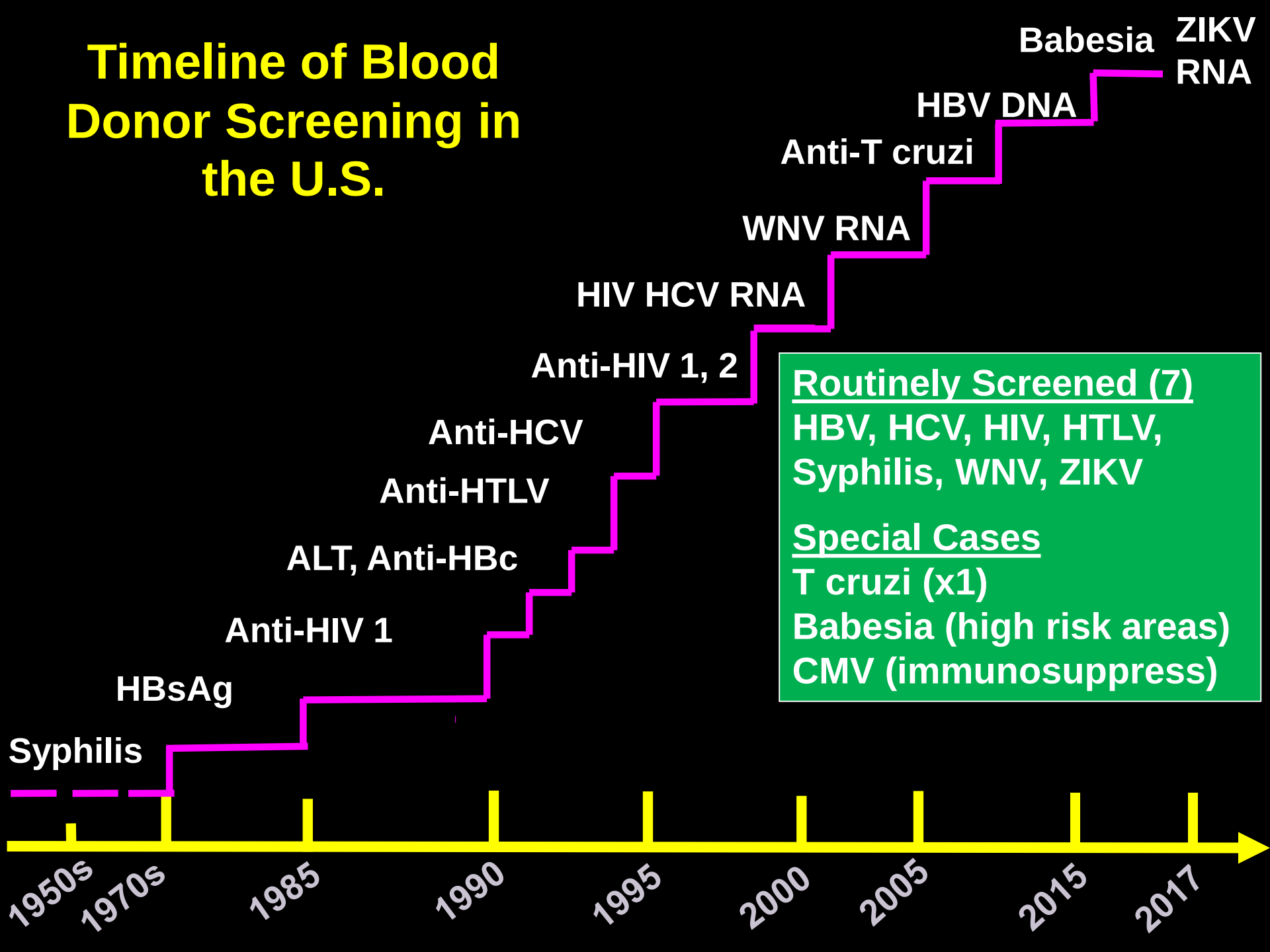
Transfusion-Transmitted HIV



Slide contributed by Dr. Harvey Alter

The Protective Triad

Timeline of Blood Donor Screening in the U.S.



Routinely Screened (7)
HBV, HCV, HIV, HTLV, Syphilis, WNV, ZIKV

Special Cases
T cruzi (x1)
Babesia (high risk areas)
CMV (immunosuppress)

What are the limitations of blood donor screening?

Strategy is typically reactive rather than preventive…

Approaches to Infectious Threats to Blood Supply

Learn from CDC, WHO, National Inquirer or other source that there is a new or emerging agent on the block that could be transfusion-transmitted

Seek evidence/proof that the agent is indeed transmitted by transfusion … If yes:

- Do nothing until magnitude of problem increases
- Defer donors based on high risk history or geography
- Add antibody or NAT test once developed & licensed

Slide adapted from Dr. Harvey Alter

Cost-of-Screening: the case of Zika virus

- **Universal individual-donor nucleic acid testing (ID-NAT) for ZIKV projected to cost $137 million per year ($109-$167 million)**
  - **Assumes $7-$13 per ID-NAT**
- **Scenarios for minipool testing range from $54 million to $132 million per year**

Ref: Ellingson KD et al, *Transfusion* 2017

Cost-of-Screening: Let's Do the Math

If universal individual-donor nucleic acid testing for ZIKV would cost $137 million/yr

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9 to 14 ZIKV+ donors in 2017 (ArboNET-AABB)

$137mil/12 mo = $11.4mil per month

x 9 mo. (Jan-Sep '17) = $102.78mil

$102.78mil/14 and $102.78mil/9

$7.3mil to $11.4 mil per ZIKV+ donor

Ref: Ellingson KD et al, *Transfusion* 2017 and Dr. Allison's iPhone

Limitations of Screening: Many Potential Threats

Screened Agents
HBV
HCV
HIV 1,2
HTLV 1,2
T pallidum (syphilis)
West Nile virus
Zika virus
Special Cases
Babesia microti
Cytomegalovirus
Trypanosoma cruzi

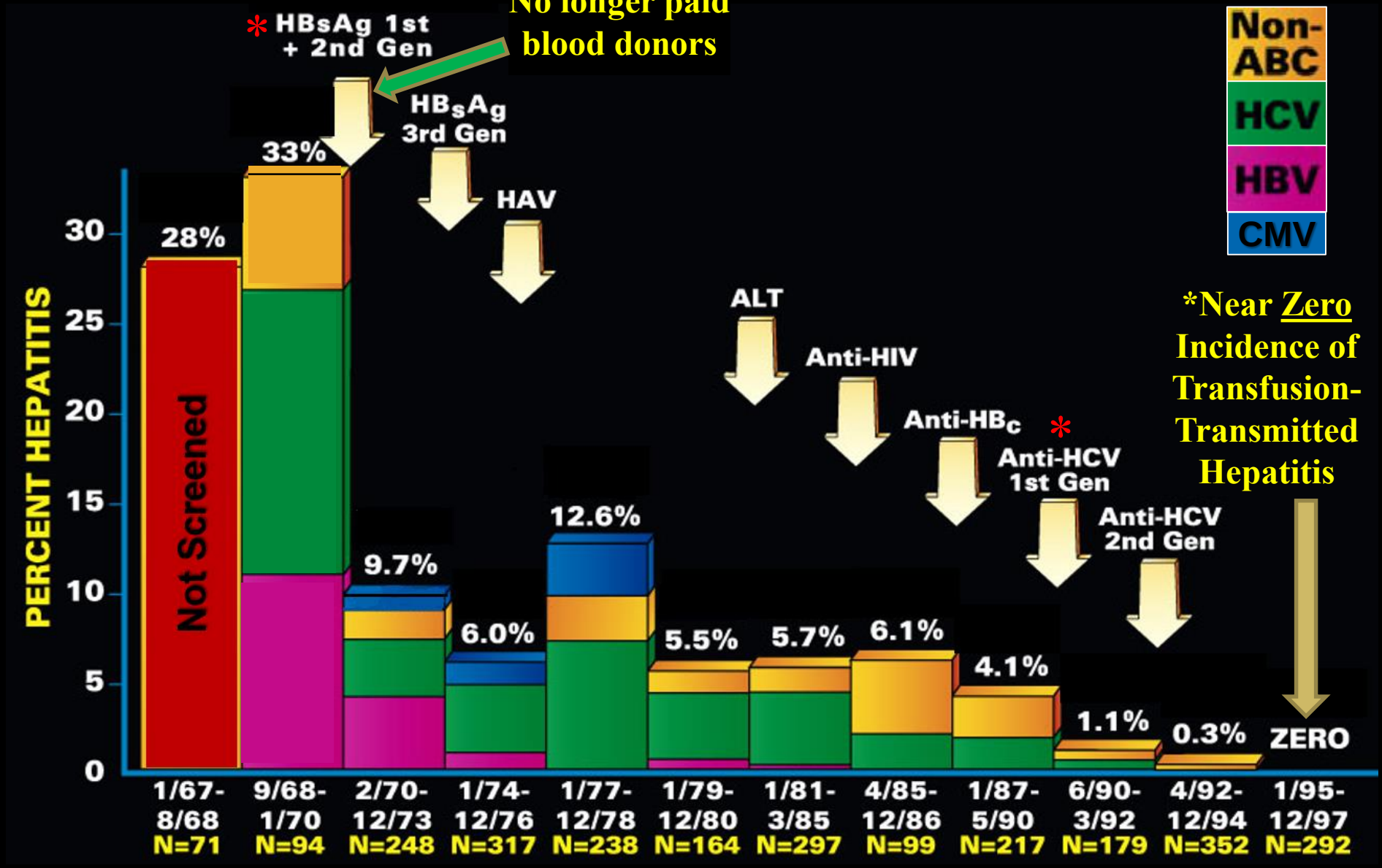
Total N = 29
Fully Screened = 7 (24%)
Not Screened = 19 (66%)

Risk	Emerging Agents*
Red	vCJD
	Dengue viruses
	Babesia species
Orange	Chikungunya virus
	St. Louis encephalitis virus
	Leishmania species
	Plasmodium species
	Trypanosoma cruzi (Chagas dx)
Yellow	Chronic wasting disease prion
	Human herpes virus 8 (KSV)
	HIV variants
	Human parvovirus B19
	Avian influenza A, H5N1
	Simian foamy virus
	Borrelia burgdorferi
	Hepatitis A virus
White	Hepatitis E virus
	Anaplasma phagocytophilum
Others	EBV
	HPV 16,18
	Rickettsia

*AABB classifications from Stramer et al, *Transfusion* 2009; also see Klein & Anstee eds. Mollison's Blood Transfusion, Chap 16

What has been the impact of blood donor screening?

Impact of Screening: Post-Transfusion Hepatitis Elimination



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What are future strategies for screening of the blood supply?

Multiplex Testing

What is Multiplex Testing?

- Screening a single patient sample for the DNA or RNA from all infectious agents at the same time
- Must be highly sensitive
- Results Must have fast turnaround time, must be adaptable for high-throughput testing, and must be inexpensive
- Must be able to add new agents rapidly for response to public health emergencies

- Requires a new regulatory approval paradigm: there is no pathway for quickly approving the addition of a new agent to a multiplex detection system

FDA-licensed Multiplex Assays for Blood Donor Testing

Tradename	Infectious Agent	Manufacturer	Specimen	Approval Date
COBAS TaqScreen MPX Test	HBV, HIV-1, HIV-2, HCV	Roche Molecular Systems, Inc. (PCR)	Plasma	12/30/08
COBAS TaqScreen MPX Test version 2.0	HBV, HIV-1, HIV-2, HCV	Roche Molecular Systems, Inc. (PCR)	Plasma	12/19/14
Procleix Ultrio Assay	HBV,HCV,HIV-1	Gen-Probe, Inc. (TMA)	Plasma/ Serum	10/3/06
Procleix Ultrio Plus Assay	HBV,HCV,HIV-1	Gen-Probe, Inc. (TMA)	Plasma/ Serum	5/25/12

- **Currently only 'Triplex' assays available: HBV, HCV, HIV**

Screened Agents
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HCV
HIV 1,2
HTLV 1,2
T pallidum (syphilis)
West Nile virus
Zika virus
Special Cases
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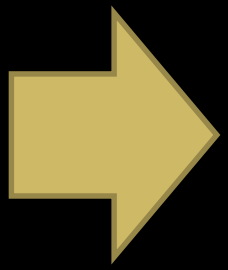
Cytomegalovirus
Trypanosoma cruzi



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*AABB classifications from Stramer et al, *Transfusion* 2009; also see Klein & Anstee eds. Mollison's Blood Transfusion, Chap 16

Multi-pathogen Detection Approaches in Development

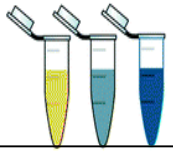
Technology	Devices
Multiplex PCR	The Light Cycler SeptiFast (Roche)
Bead-based systems	Luminex xMAP
	Barcoded, magnetic beads
	Target-enriched multiplex PCR (Diatherix)
DNA Microarrays	ViroChip
	Universal detection array
	GreenChip
	Lawrence Livermore
	Resequencing microarrays (TessArae, Inc.)
Multiplex PCR with mass spectrometry identification	Plex-ID (Abbott Ibis Biosciences)
Multiplex PCR with nanoparticle T2 magnetic resonance for detection	T2 Magnetic resonance (T2 Biosystems, Inc.)
Isothermal multiplex amplification	Loop-mediated isothermal amplification
	Recombinase polymerase amplification
Next-generation sequencing	Ion Torrent PGM (Life Technologies, Inc.), Miseq (Illumina),454-Titanium (Roche)
Spatial multiplexing of real-time PCR	TaqMan OpenArray (Life Technologies, Inc.)

Duncan R et al. *Expert Rev Mol Diagn*. 2016

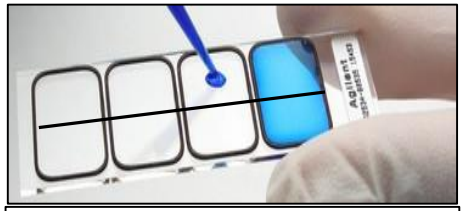
DTM Microarray Approach – Specific for Transfusion-Transmitted Agent Detection

1. Clinical Sample

2. Nucleic acid extraction and reverse transcription



3. Random PCR amplification and coupling to fluorescent dyes

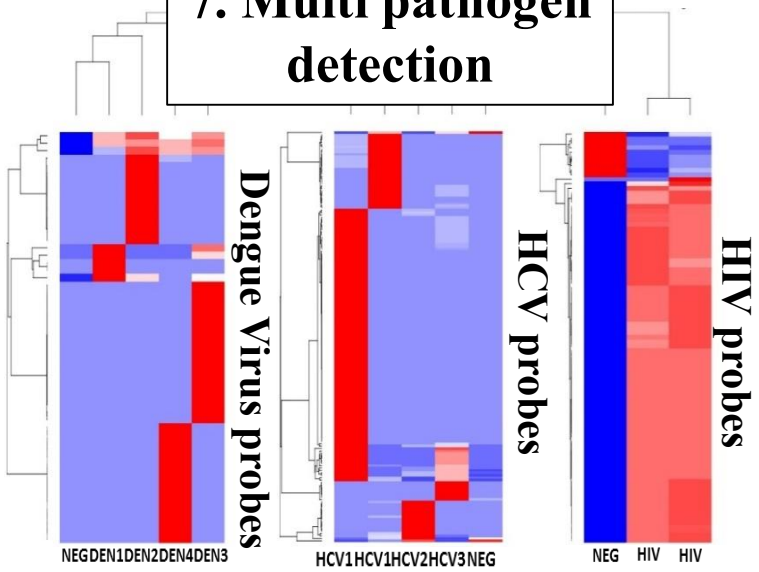


4. Hybridization to customized pathogen chip

5. Signal detection

6. Analysis

7. Multi pathogen detection



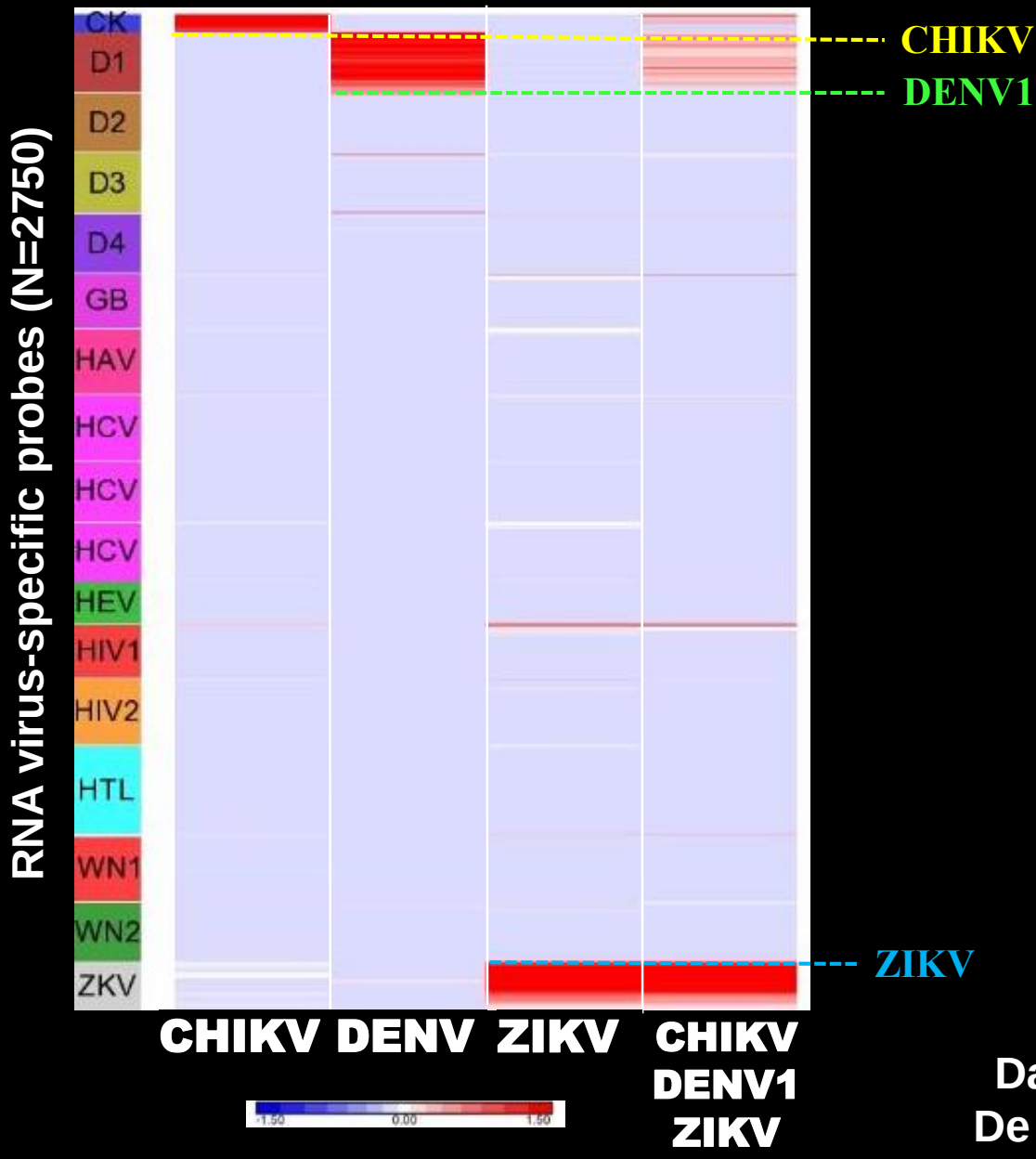
Slide adapted from Dr. Valeria De Giorgi

CC/DTM/IDS RNA Chip Performance

Sample	Source	Lowest Conc. Tested	Signal Detection
HCV1	Positive Plasma	≥1 x 10^4 IU/ml	Y
HCV2	Positive Plasma	≥1 x 10^4 IU/ml	Y
HCV3	Positive Plasma	≥1 x 10^4 IU/ml	Y
HIV1	Positive Plasma	≥1 x 10^4 copies/ml	Y
HIV2	Positive Plasma	≥1 x 10^4 copies/ml	Y
DENV1	Positive Plasma	≥1 x 10^3 copies/µL	Y
DENV2	Positive Plasma	≥1 x 10^3 copies/µL	Y
DENV3	Positive Plasma	≥1 x 10^3 copies/µL	Y
DENV4	Positive Plasma	≥1 x 10^3 copies/µL	Y
WNV	ViroCell Genomic RNA	≥1 x 10^4 copies/µL	Y
HAV	Positive Plasma	≥1 x 10^3 copies/µL	Y
HEV	Positive Plasma	≥1 x 10^3 copies/µL	Y
DENV1	Positive Plasma	≥1 x 10^3 copies/ml	Y
CHIKV	Positive Plasma	≥1 x 10^3 copies/ml	Y
ZIKV	Positive Plasma	≥1 x 10^3 copies/ml	Y
CHIKV+DENV+ZIKV	Positive Plasma	≥1 x 10^3 copies/µL	Y

Data from Dr. Valeria De Giorgi, Infectious Diseases Section, NIH/CC Dept. of Transfusion Medicine

Detection of CHIKV, DENV, ZIKV Alone and in Combination at 10^3 copies/mL



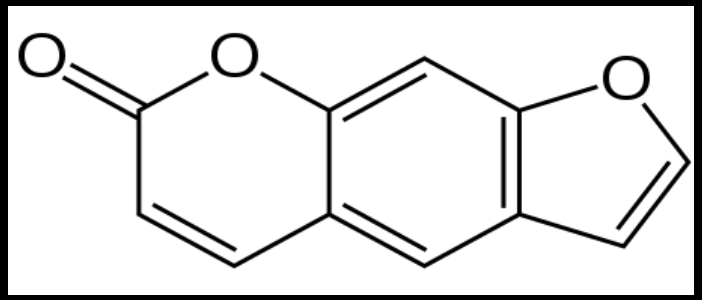
Data from Dr. Valeria De Giorgi CC-DTM-IDS

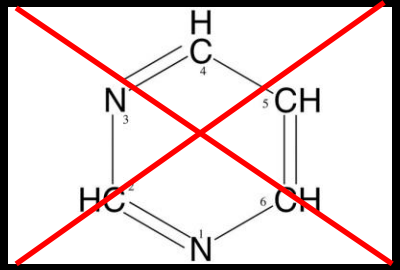
The Protective Triad

What Methods are used to Inactivate Pathogens in Blood Products?

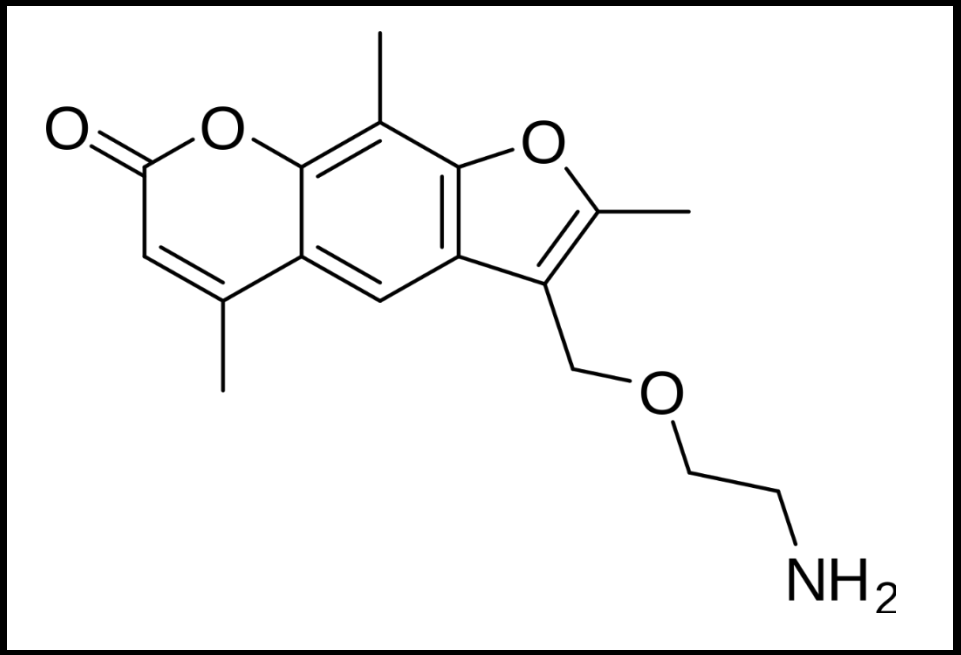
Damage Nucleic Acids of Infectious Agents

Psoralen



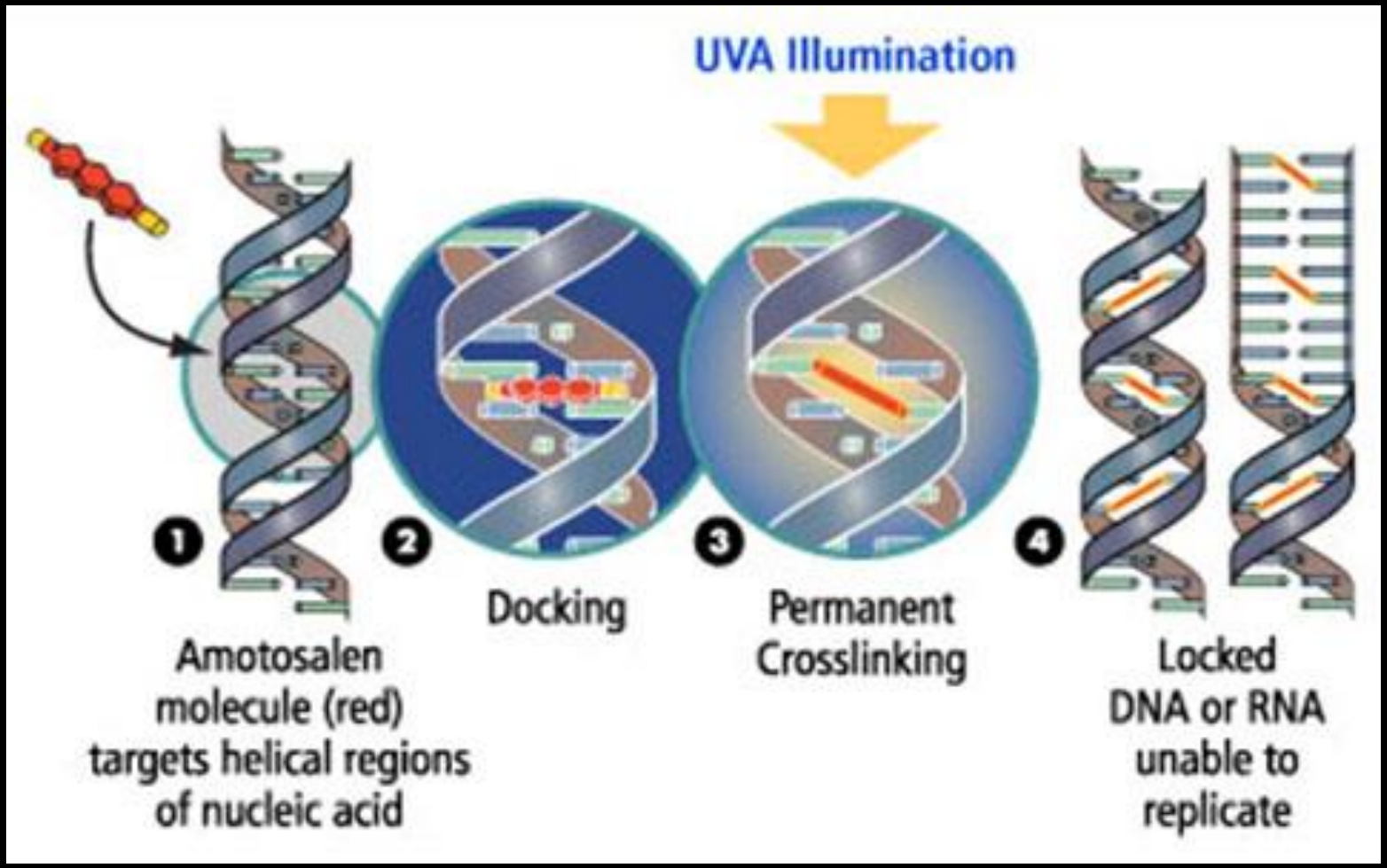


Amotosalen (Intercept)



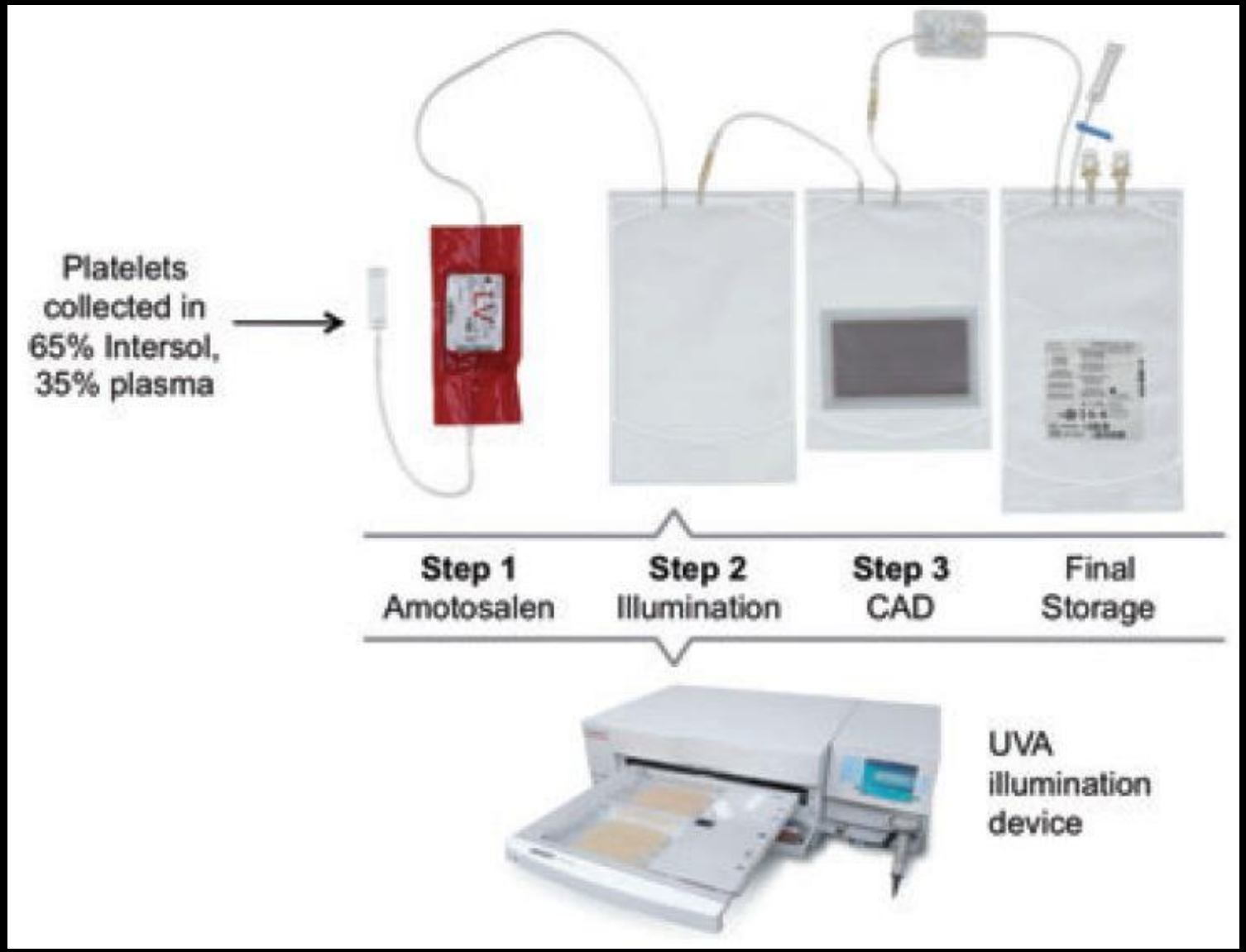
- **NIH Dept. of Transfusion Medicine uses Intercept for treatment of platelets (only system FDA-approved in U.S.)**

Damage Nucleic Acids of Infectious Agents



- **Intercalates into DNA, with UVA exposure, forms monoadducts and covalent interstrand cross-links with thymidines and cytosines** (pyrimidines)

Damage Nucleic Acids of Infectious Agents



CAD, Compound Adsorption Device

Stramer et al, *Transfusion* 2009

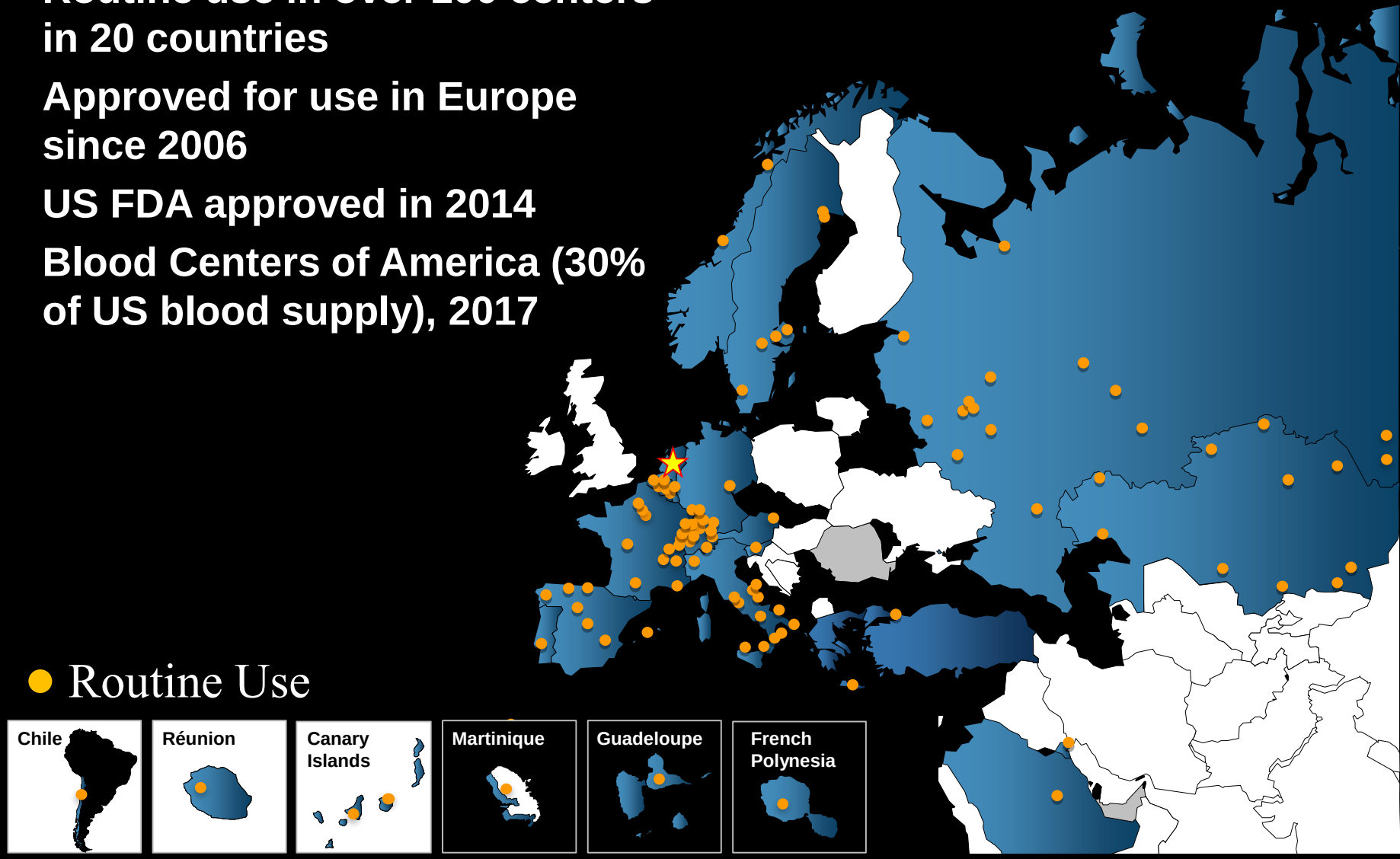
Inactivation of Infectious Agents in Plasma and Platelets with Amotosalen/UVA

Classification	Agents	Log Reduction
Viruses, Enveloped	HIV-1/2, HTLV-I/II, HBV, HCV, WNV, CMV, SARS-CoV, Vaccinia	>4.5 - >6.8
Viruses, Non-Enveloped	Hum.Adeno-5, Bluetongue Parvo B-19, HAV	>5.1 - >6.8 3.5 - >5.0
Bacteria	Gram + & Gram-	>7.3
Spirochetes	T. pallidum, B. burgdorferi	>5.9 - >10.6
Protozoa etc	P. falciparum, T. cruzi, B. microti	>5.0 - >6.9

Slide adapted from Dr. Harvey Alter

Intercept Platelet and Plasma Use

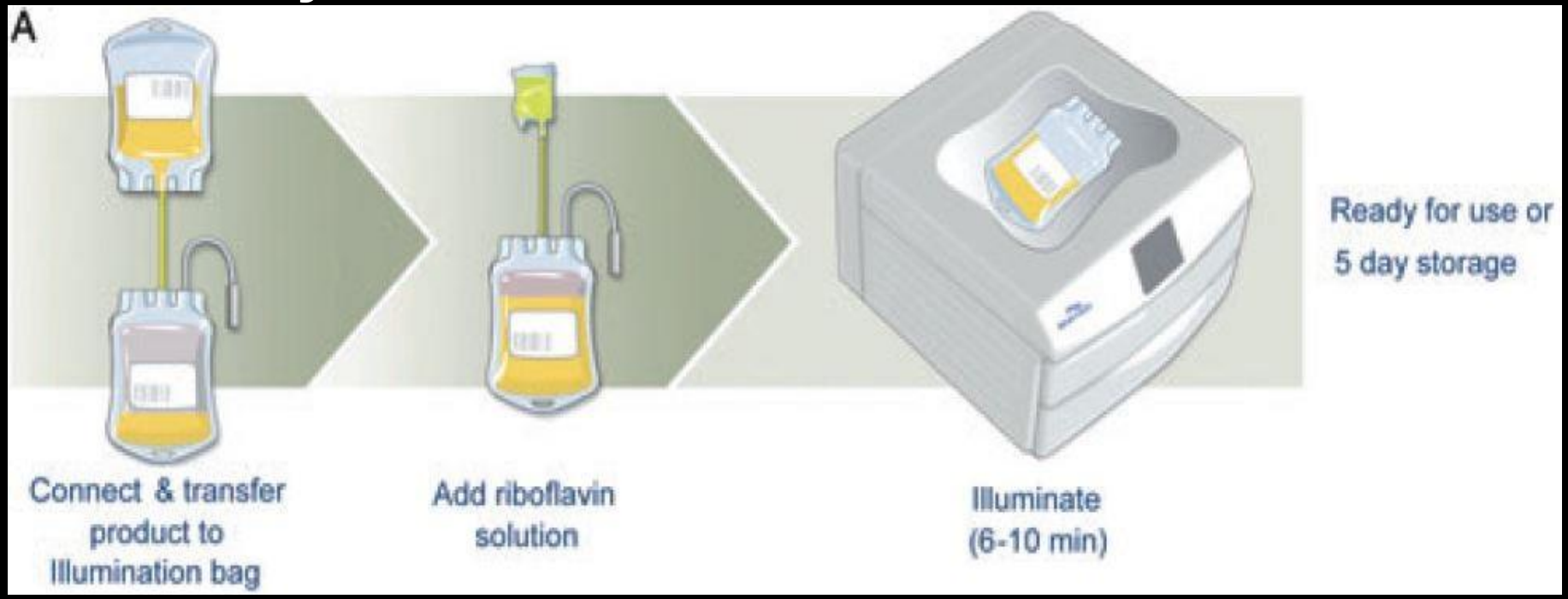
- Routine use in over 100 centers in 20 countries
- Approved for use in Europe since 2006
- US FDA approved in 2014
- Blood Centers of America (30% of US blood supply), 2017



Slide provided by Dr. Harvey Klein

Damage Nucleic Acids of Infectious Agents

Mirasol System



- **Riboflavin (B2) binds to nucleic acids and UV (B > A) light activation oxidizes guanine nucleotides**
- **Mirasol tx of whole blood in Ghana sig. reduced transfusion-transmitted malaria (treated 1/28, 4% vs. controls 8/37, 22%; P=0.039)**

Stramer et al, *Transfusion* 2009; Allain et al, Effect of Plasmodium inactivation, *Lancet* 2016

ADVANTAGES OF PATHOGEN REDUCTION

- Effectively inactivates most clinically relevant viruses whether RNA or DNA, ss or ds, enveloped or non-enveloped, intra-cellular or extra-cellular
- Inactivates virtually all clinically relevant gram+ and gram- bacteria
- Inactivates all the spirochetes, rickettsia and protozoa of known transfusion relevance
- Offers probable preemptive protection against pathogenic, potentially lethal, agents that will inevitably emerge in the future
- Fewer platelet transfusion reactions with INTERCEPT platelets than with conventional platelets

LIMITATIONS OF PATHOGEN REDUCTION

- Currently licensed only for platelets and plasma (most transfusions are RBC)
- Decreased platelet yield (10-30%) observed in clinical trials
  - Systems improvements resulted in improved processing yields with minimal differences in count increment or transfusions per patient
- Insufficient kill of some hi-titer agents (HAV, Parvo B-19)
- Does NOT inactivate prions, vCJD
- Toxicity: theoretical for psoralens at very low residual doses transfused; None known for riboflavin; very wide safety margin
- Cost: The elephant in the room

Potential Cost-Savings per Unit with Pathogen Inactivation

OFFSETS TO COST FOR PATHOGEN REDUCTION

- Eliminate bacterial testing
- Eliminate product irradiation
- Extend platelet shelf life to 7-days
- Eliminate some current assays
- Preempt testing of emerging agents
- Reduce donor exclusions based on geography

TABLE 6. Summary of potential monetary impact of INTERCEPT PLTs

Test or procedure	Procedure mean amount $	
Eliminated		
Bacterial testing	19.90	
PoR	30.32	
WNV	8.90	
CMV	5.56	
*T. cruzi**	14.58	
Syphilis	7.08	
Subtotal*		71.76
Procedures eliminated		
Irradiation	8.50	
Transfusion reactions work-up	2.70	
Subtotal		11.20
Test avoided		
Dengue	20.90	
Babesia	20.90	
Subtotal		41.80
Additional from 7-day storage		16.89
Additional savings from products not discarded due to false-positive tests		1.27
Total*		$142.92

* *T. cruzi* is not included in the total.

McCullough et al. *Transfusion* 2015

Acknowledgements

Dr. Harvey J. Alter

- Mentor > 13 years
- Eliminator of post-transfusion hepatitis

- Patients and Research Participants
- Infectious Diseases Section including Dr. Valeria De Giorgi, Pathogen Chip Develop. Lead
- Dept. of Transfusion Medicine
- NIH Clinical Center

Non-Infectious

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